ADVANCED-1 (Phase 1a/b) and ADVANCED-2 (Phase 1b/2) Study of Intravesical Instillation of TARA-002 in Adults with High-grade Non-muscle Invasive Bladder Cancer

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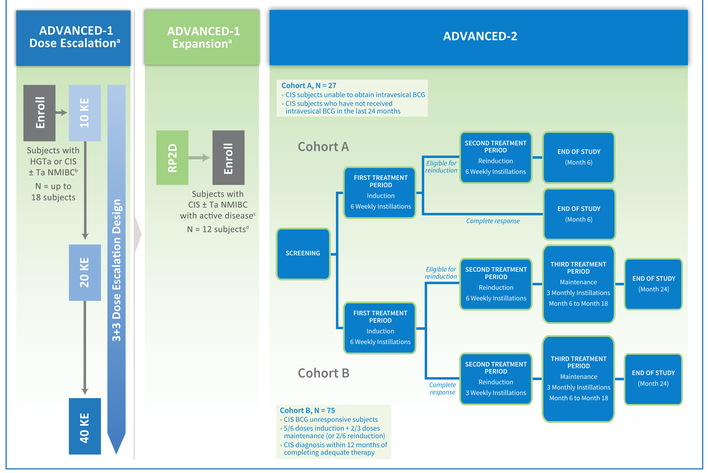
INTRODUCTION AND OBJECTIVE

- Bladder cancer is the most common malignancy involving the urinary system, resulting in ~18,000 US deaths/year[1]
- Bladder cancer is the 6th most common cancer in the United States, with NMIBC representing approximately 80% of bladder cancer diagnoses[2,3]
- With the current Bacillus Calmette-Guérin (BCG) shortage and limited effective alternative therapies, there continues to be a significant unmet need for treatment options for patients with NMIBC
- TARA-002 is a lyophilized biological preparation for instillation containing cells of *Streptococcus pyogenes* (Group A, type 3) Su strain treated with benzylpenicillin and is being developed for the treatment of high-grade (HG) NMIBC
- TARA-002 is manufactured using the same master cell bank as OK-432 (Picibanil®)
- OK-432 is approved in Japan and Taiwan for the treatment of several oncology indications
- The antitumor activity of TARA-002 and OK-432 is thought to occur by direct cytotoxicity and by stimulation of immunocompetent cells (including T cells and natural killer cells) through the induction of helper T-cell type-1 cytokines (including interferon gamma and various interleukins), which then recruit cytotoxic T lymphocytes to tumor cells[3,4]

METHODS

FIGURE 1. STUDY DESIGN



Abbreviations: BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; HGTa, high-grade Ta; KE, Klinische Einheit; NMIBC, non-muscle invasive bladder cancer; RP2D, recommended Phase 2 dose.

[a]Subjects will receive weekly intravesical doses of TARA-002 instillation for 6 weeks.

[b]Subjects with HGTa or CIS ± Ta NMIBC who are unable to obtain intravesical BCG, received ≥ 1 dose of intravesical BCG, or received ≥ 1 dose of intravesical chemotherapy.

[c]Defined as disease present at last tumor evaluation prior to signing ICF.

[d]Subjects enrolled in the dose expansion phase will not include subjects previously enrolled and treated in the dose escalation phase.

ADVANCED-1

- ADVANCED-1 is a Phase 1a dose escalation and Phase 1b dose expansion open-label study of intravesical TARA-002 in adults ≥ 18 years with HG Ta or CIS ± Ta
- Includes up to 18 subjects enrolled at cohorts of increasing dose levels (10 KE, 20 KE, 40 KE) in a 3+3 design, followed by a dose expansion phase in 12 CIS patients (**Figure 1**)
- The study duration is 12-14 weeks per subject, including the induction period

ADVANCED-2

- ADVANCED-2 is a Phase 1b/2 dose expansion, open-label study of intravesical TARA-002 in adults ≥ 18 years with CIS ± Ta/T1
- This study includes ~102 subjects enrolled in 2 cohorts based on prior BCG experience (**Figure 1**):
  - Cohort A includes:
    - 27 subjects with CIS (± Ta/T1) who are unable to obtain intravesical BCG, or
    - Subjects with CIS (± Ta/T1) who have not received intravesical BCG for 24 months prior to CIS diagnosis
  - Cohort B includes:
    - 75 subjects with CIS (± Ta/T1) BCG unresponsive after completion of adequate BCG therapy (minimum of 5/6 doses induction and 2/3 doses maintenance or 2/6 doses reinduction)
  - The study duration is:
    - 6 months per subject for Cohort A (includes induction, reinduction [if applicable])
    - 24 months per subject for Cohort B (includes induction; reinduction [if applicable]; maintenance until 18 months)

STUDY OBJECTIVES/ENDPOINTS

ADVANCED-1

- The purpose of the ADVANCED-1 dose escalation study is to evaluate the safety and toxicity of TARA-002 and to establish the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) in the treatment of HGTa or CIS NMIBC (including CIS with concomitant Ta)
- The purpose of the ADVANCED-1 Expansion study is to further assess the safety and preliminary anti-tumor activity of TARA-002 in the treatment of subjects with CIS NMIBC with active disease
- Primary Endpoints:
  - ADVANCED-1 Dose Escalation
    - Incidence of dose limiting toxicity (DLT) adverse events (AEs) in subjects with HGTa or CIS NMIBC (including CIS with concomitant Ta)
    - MTD and RP2D of TARA-002 in subjects with HGTa or CIS NMIBC (including CIS with concomitant Ta)
  - ADVANCED-1 Expansion
    - Incidence of AEs in subjects with CIS NMIBC with active disease

ADVANCED-2

- The purpose of the ADVANCED-2 Phase 1b/2 dose expansion study is to assess the safety and anti-tumor activity of TARA-002, at the established RP2D, in the treatment of subjects with CIS (± Ta/T1) NMIBC with active disease
- Primary Endpoint:
  - Incidence of high-grade complete response at any time
- Safety Endpoints:
  - Incidence and severity of AEs
  - Incidence and severity of treatment emergent AEs (TEAEs)
  - Incidence and severity of serious AEs (SAEs)
  - Incidence and severity of treatment emergent SAEs (TESAEs)

ADVANCED-2 ELIGIBILITY

TABLE 1. KEY INCLUSION AND EXCLUSION CRITERIA

Key Inclusion Criteria

- CIS ± Ta/T1 (active disease present at last tumor evaluation prior to signing consent)
- Cohort A – BCG naïve or BCG exposure > 24 months prior to CIS diagnosis
- Cohort B – CIS BCG unresponsive
- For CIS with concomitant Ta/T1, all visible papillary tumors must be removed prior to treatment

Key Exclusion Criteria

- Penicillin allergy
- Concomitant prostatic or upper tract urothelial involvement per Investigator's assessment
- Has significant urinary incontinence or otherwise unable to hold intravesical immunotherapy in the bladder for 2 hours
- Participation in any other anti-cancer therapy (including investigational agents) within 6 weeks prior to signing informed consent

- The key inclusion and exclusion criteria are summarized in **Table 1**

ADVANCED-1 DOSE ESCALATION RESULTS

TABLE 2. ADVANCED-1 DOSE ESCALATION, OVERVIEW OF EXPOSURE, AND DEMOGRAPHICS (PHASE 1A)

	COHORT 1	COHORT 2	COHORT 3
EXPOSURE			
No. of Subjects Exposed	3	3	3
Dose Level	10 KE	20 KE	40 KE
DEMOGRAPHICS			
Age (mean, range)	73 (66-80)	62 (42-76)	77 (71-82)
Sex (number)			
Male	1	2	2
Female	2	1	1
Ethnicity (number)			
White, not Hispanic or Latino	3	3	3

- In the ADVANCED-1 dose escalation study, 9 subjects have been enrolled in 3 separate cohorts of increasing dose levels (3 subjects per cohort)
  - Cohort 1: 10 KE, Cohort 2: 20 KE, Cohort 3: 40 KE
- Cohort 1: 3 subjects (1 male; 2 female) 66-80 yrs have completed treatment with TARA-002 at 10 KE (**Table 2**)
- Cohort 2: 3 subjects (2 male; 1 female) 42-76 yrs have completed treatment with TARA-002 at 20 KE (**Table 2**)
- Cohort 3: 3 subjects (2 male; 1 female) 71-82 years have completed treatment with TARA-002 at 40 KE (**Table 2**)
- Across all 3 cohorts, 8 of 9 patients experienced related TEAEs
  - All related TEAEs were Grade 1 and Grade 2
    - The most frequently reported related TEAEs included urinary urgency, urinary frequency, urinary tract pain/burning, and bladder spasm, and mostly resolved in a few hours to a few days
    - The most frequently reported non-urinary symptoms were fatigue, headache, and chills. These events resolved without treatment or after the use of antipyretics/analgesics
  - No subjects experienced Grade 3 or higher TEAEs, TESAEs or DLTs
- No DLTs were reported across the 3 dose levels (10 KE, 20 KE, 40 KE)
- A MTD was not determined, and dose escalation will continue in exploratory cohorts; the 40 KE dose has been determined to be RP2D and will be the dose studied in additional clinical trials

CONCLUSIONS

- The RP2D of TARA-002 has been established in the ADVANCED-1 dose escalation study in patients with high-grade NMIBC at 40 KE
  - No DLTs were reported at the established RP2D
- The ADVANCED-1 dose expansion study is ongoing and will provide further evidence of safety and initial anti-tumor activity of TARA-002 in patients with high-grade CIS NMIBC at the 3-month timepoint at the established RP2D of 40 KE
- The ADVANCED-2 study will provide further evidence of safety and anti-tumor activity of TARA-002 in patients with high-grade CIS ± Ta/T1 NMIBC

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